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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/603,385	06/24/2003	Fen Zhang	41812-8001.US00	3044

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,385	ZHANG, FEN	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/23/05 has been entered.

Claim 11 was canceled as requested.

Claims 1-10 and 12-20 remain pending, and the elected invention of "growth factors" and "amniotic membrane" are under consideration in this Office Action.

Priority

Priority is claimed in the first line of the specification to provisional application 60/391,550, filed 6/24/2002. The effective filing date of the application is considered to be 6/24/2002.

Rejections Withdrawn

The rejection of claims 9 and 16-20 for indefiniteness is withdrawn in view of Applicnat's amendment.

The rejection under 35 USC 102 of claims 1-10, 12, and 14-20 over Sakuragawa is withdrawn in view of applicant's amendment requiring a reconstituted tissue membrane. Sakuragawa does not teach a reconstituted tissue membrane.

Claim Objections

Claim 8 is objected to because it lacks a conjunction between "animal cells" and "mammalian cells". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-10 and 12-20 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compositions for delivering a growth factor to a wound in the skin of a patient by administering to the wound site amniotic epithelial cells that secrete the growth factor, does not reasonably provide enablement for obtaining desired effects other than wound healing, for delivering molecules other than growth factors, or for methods of delivering molecules to sites other than the site of cell administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods and compositions for delivering a molecule to a patient comprising administering to the patient amniotic epithelial cells, wherein said cells are capable of delivering the molecule. The specification defines the term patient

as the recipient of the molecule to be delivered regardless of the purpose of such delivery (detailed description paragraph 74), so the claims are not limited to medical treatment. Although the specification is largely devoted to the treatment of wounds, the claims are not limited to this purpose. For example, the narrowest claims that recite any purpose for delivery of a molecule are claims 4 and 5, which are drawn to the delivery of an effective amount of a molecule useful for achieving any therapeutic, cosmetic, prophylactic, or diagnostic effect without limitation. So, the claims can reasonably be interpreted as embracing methods and effects as diverse as the treatment and cure of melanoma, eczema, psoriasis, and wound healing. The claims are not limited to the delivery of peptides or polypeptides, but embrace the delivery of any molecule without limitation to the skin for the purpose of eliciting any desired effect.

The specification provides no working example of the delivery of any molecule to a patient through the use of amniotic epithelial cells. No guidance is presented as to how to deliver any type of molecule other than a secretable gene product. No guidance is presented with regard to how many amniotic epithelial cells must be transfected with what type of expression construct to achieve the appropriate level of expression of any specific gene product for any specific desired effect. Instead the specification teaches a working example in which an amniotic membrane is stripped of its epithelium, reconstituted with Madin-Darby Canine Kidney (MDCK) cells that stably express PDGF-beta, and applied to a rabbit chronic wound model. Accelerated healing is reported. However, as noted above, the claims are in no way limited to wound healing, but embrace delivery of any molecule to the skin of any patient for the diagnosis or

treatment of any cosmetic or medical condition. The specification provides no guidance at all regarding how much expression is required of any of the 52 species of molecules recited in claim 7 for any therapeutic, cosmetic, or prophylactic purpose, e.g. for the treatment of melanoma. As noted above, the specification also fails to provide any guidance as to how to use the claimed invention to deliver any molecule other than a polypeptide or a peptide.

The full scope of the claims relating to obtaining therapeutic, cosmetic, and prophylactic effects by delivery of genetically modified cells that express a desired polypeptide or peptide is not fully enabled due to a lack of guidance. This art was recognized as highly unpredictable at the time of filing, and the specification fails to provide the guidance that is missing from the prior art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). With specific regard to ex vivo therapy using retroviral vectors, Verma taught that expression of transgenes was shut off within five to seven days, even in animals lacking a functional immune system. Verma also points out that the search for an appropriate enhancer-promoter combination is a case of trial and error for each given type of cell. See page 240, column 2, lines 10-1, and sentence bridging columns 2 and 3. Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no

conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21.

However, the prior art taught that wound healing may be facilitated by the delivery to a wound of expression vectors encoding growth factors. See e.g. US Patent 5962427, claims 1-14, and especially claims 6-11. Furthermore, the prior art taught that epithelial cells may be transfected with expression vectors encoding growth factors, applied to a membrane, and administered to a wound to improve healing. For example, Eming (Invest. Dermatol. 105(6): 756-763, 1995) taught that grafts of keratinocyte monolayers retrovirally modified to overexpress PDGF-A aided in tissue regeneration when administered to the skin of immunodeficient (athymic) mice. See abstract, and page 757, column 2, fourth full paragraph. These results were reproduced by Eming et al (Biotech. Bioeng. 52: 15-23, 1996), see abstract and page 19, column 1, first full paragraph, and column 2, first full paragraph. As a result methods of improving wound healing by administration of epithelial cells modified to express growth factors is considered to be enabled.

However, the specification does not enable the treatment of wounds, or any other therapeutic, prophylactic, cosmetic, or diagnostic effect by delivery of molecules other than growth factors, as there is no guidance whatsoever as to how to use amniotic epithelial cells to deliver any molecule other than a peptide or polypeptide. The specification also provides no guidance at all regarding treating such diverse diseases as melanoma, eczema, or psoriasis with any molecule, although these treatments are embraced within the metes and bounds of the claims. The specification also provides inadequate guidance as to how to improve wound healing with molecules other than growth factors. Wound healing is recognized as a very complex process involving intricate interactions between a variety of cell types, structural proteins, growth factors, and proteinases. (Stadelmann, W.K., et al., Am J Surg 176(Supp 2A):26S-38S, (1998)). Some of the factors involved in wound healing may affect more than one aspect of the process. So, when a therapeutic regime is contemplated for impaired wound healing, the various process involved in wound healing, i.e. inflammation, angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling, must be critically considered, and an accurate diagnosis of the factors impairing wound healing must be made. See Eming et al (Cells, Tissues, Organs (2002) 172(2): 105-117) page 106, column 2, first full paragraph. The specification provides no guidance as to the appropriate level of expression of any gene product, nor how to obtain and limit expression within such limits. For example, although the specification suggests the use of anti-inflammatory proteins, it provides no guidance as to how much expression of any anti-inflammatory protein is therapeutic.

This is a critical omission in view of the fact that it is recognized in the specification and the prior art that inflammation is a normal part of wound healing. Indeed, Eming (2002) taught that impairment of inflammation could cause inadequate angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling. It follows that overexpression of anti-inflammatories could actually impede wound healing.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic, cosmetic, diagnostic, or prognostic effect. However, the specification does not provide such guidance and fails to provide any correlation between vectors, cells comprising vectors, dosage amounts, therapeutic genes other than growth factor genes, and any specific disease or condition treatable by the nucleic acids or cells comprising such as disclosed in the instant specification. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

Response to Arguments

Applicant's arguments filed 5/23/05 have been fully considered but they are not persuasive. At page 5 of the response Applicant submits that the rejection is moot. This is unpersuasive in the absence of any explanation as to why the rejection is moot.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-10, 12, 13, 16-18, and 20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Faulk et al (Lancet 1(8179): 1156-1158, 1980) as evidenced by Uchida et al (J. Neurosci. Res. 62: 585-590, 2000).

Faulk taught a method of treating burned skin by application of amniotic basement membrane comprising cultured amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs. Inasmuch as the cells of Faulk are composed of molecules, Faulk teaches the delivery of molecules to skin of a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J. Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract. Absent evidence to the contrary, the epithelial cells of Faulk are considered to secrete NGF as well. Further evidence that the cells produce growth factors is the fact that Faulk observed increased angiogenesis as a result of the graft. As noted by Faulk at page 1157, column 2, first full paragraph, this may be due to the secretion of angiogenic factors from the amnion.

Independent claims 1 and 16 require cells "genetically modified to deliver" a molecule. Both of these claims are further limited by dependent claims that specify that

the cells must be "engineered to include an exogenous polynucleotide" (i.e. claims 6 and 19). In view of this further limitation, the scope of the phrase "genetically modified" is interpreted to embrace a greater breadth than "engineered to include an exogenous polynucleotide." The specification does not define the limits of "genetically modified", so it is given its broadest reasonable interpretation and is deemed to include such processes as chemical mutagenesis and meiotic recombination. All amniotic cells are derived ultimately from zygotes produced by the fusion of gametes that have undergone meiotic recombination. So, all amniotic epithelial cells have undergone genetic modification. As a result, Faulk anticipates the limitation "genetically modified to deliver said molecule."

The claims also require a "reconstituted tissue membrane". This phrase is not given a limiting definition in the specification, and it is not clear how the structure of a reconstituted tissue membrane differs from the membrane of Faulk. Absent evidence to the contrary, they are the same.

Thus Faulk anticipates the claims.

Claims 16-19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996).

This rejection is directed to a generic embodiment of the rejection which does not require amniotic epithelial cells and an amniotic membrane.

Eming taught a composition comprising keratinocytes genetically modified to secrete a biologically effective amount of PDGF-A. The cells were grown in culture to

form a monolayer about 4-7 cells thick. This is considered to be a reconstituted tissue membrane. The monolayer membrane was then attached to a silastic support. The support bearing the membrane was applied topically to the bottom of the skin via a full thickness skin flap. See abstract, and page 17, column 1, second paragraph under the heading "Grafting". Thus Eming anticipates the claims.

Response to Arguments

Applicant's arguments filed 5/23/05 have been fully considered but they are not persuasive.

The Faulk and Eming references are addressed at pages 6 and 7 of the response. Applicant asserts that Faulk does not teach the claimed invention. However, as discussed above, Faulk teaches a method of delivering a molecule to the skin of a patient by topically administering amniotic epithelial cells to the skin of said patient wherein the cells are genetically modified by meiotic recombination, and are part of a structure that is indistinguishable from a reconstituted tissue membrane. Applicant argues essentially that the cells of Faulk do not deliver molecules to cell the skin of the patient. Applicant is arguing a limitation that is not in the claims. The method requires delivering a molecule to the skin of the patient by administering amniotic epithelial cells to the skin of the patient. There is no requirement that the molecule must be delivered by the cell. Because the cell comprises molecules, and is delivered to the skin, molecules are necessarily delivered to the skin by administering the cell. In any event, Uchida showed that amniotic epithelial cells secrete NGF, and Applicant has not

explained how the cells of Faulk could fail to deliver NGF to the cells of the patient when applied to the skin of the patient, so the rejection is maintained.

Regarding the rejection of claims 16-19 over Eming, Applicant argues that Eming fails to teach topical application of amniotic epithelial cells, and points out that the cells are inserted under a full thickness skin flap. The Examiner is aware that the elected species under examination is amniotic epithelial cells. However, as noted above, the Eming reference was used to reject a more generic version of the claimed invention in order to demonstrate that the generic version of the claim is not allowable. Note that claims 16-19 are not limited to amniotic epithelial cells, but are drawn more broadly to "cells" in general. The Eming reference was applied against this embodiment, rather than the elected embodiment of amniotic cells. Regarding topical application, it is noted that Stedman's Medical Dictionary (retrieved from the web at http://www.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.Stedmans on 7/26/05) defines "topical" as "relating to a definite place or locality; local", and the Merriam Webster's Collegiate Dictionary, 10th Edition 1997 defines "topical" as "designed for or involving local application and action". As such, "topical" application is considered to be "local" application. Absent evidence to the contrary, Eming's insertion of a membrane under a full thickness skin flap results in local delivery of PDGF to the underside of the skin, and represents topical application. So, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996) and Sakuragawa (US Patent 6117676, issued 9/12/00).

Faulk taught a method of treating wounded skin by application of amniotic basement membrane comprising human amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs.

Faulk did not teach amniotic epithelial cells engineered to include an exogenous polynucleotide.

Eming taught a method of promoting growth and vascularization in a wound by delivering PDGF-A to a patient. Epithelial keratinocytes were genetically modified with a retrovirus to express PDGF-A, and were attached to a supporting membrane and administered to the skin of an immunodeficient (athymic) patient, resulting in improved growth and vascularization in the wound. See abstract, and page 17, column 1, second paragraph under the heading "Grafting". Eming's goal was to enhance the function of cells used in skin substitutes by genetic modification to produce a cell-based vehicle for the local synthesis and delivery of wound-healing growth factors.

Sakuragawa taught that amniotic epithelial cells could be transfected by either plasmid or adenoviral vectors, and that amniotic epithelial cells do not express HLA-A, B, C and DR antigens and do not cause rejection reactions or topical inflammation even when transplanted allogeneically. See column 2, lines 9-13 and 27-39; column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Faulk by transfecting the amniotic epithelial cells with the vector of Eming. One would have been motivated to do so because Eming shows that delivery of PDGF-A by transfected epithelial cells attached to a membrane results in tissue regeneration. One would have selected amniotic epithelial cells because Sakuragawa teaches that these cells can be conveniently transplanted allogeneically without rejection due to the absence of cell surface HLA class II antigens, and a much diminished amount of HLA class I antigens, and because it was routine in the art at the time of the invention to apply to wounds such as ulcers amniotic membranes comprising amniotic epithelial cells. This would allow study of the healing process in immune-competent animals without instigation of inflammation beyond that which is ordinarily associated with wound healing. Also, Sakuragawa demonstrates that these cells can be transfected by means of viruses or plasmids, and suggests their use in therapeutic applications involving administration of the cells to skin. Finally, using cells on an amniotic membrane, as taught by Faulk, eliminates the step of applying cells to a synthetic membrane, thereby simplifying the procedure of Eming.

Thus the invention as a whole was prima facie obvious.

Claims 1-10 and 12-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996), Sakuragawa (US Patent 6117676, issued 9/12/00), and Pollock et al (US Patent 6191269, issued 2/20/2001).

The teachings of Faulk, Eming, and Sakuragawa are discussed above and can be combined to render obvious methods and compositions for delivering molecules to a patient by genetically modifying amniotic epithelial cells to produce the molecule, and administering the amniotic epithelial cells on an amniotic membrane. These references teach the use of retroviral, plasmid, and adenoviral vectors for transfection of epithelial cells.

These references do not teach the use lentiviral vectors, adeno-associated virus, or cosmid vectors to transfect .

Pollock taught that plasmids, cosmids, retroviral vectors, lentiviral vectors, adenoviral vectors, and adeno-associated viral vectors could be used interchangeably as expression vectors in eukaryotic cells. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). As such, it would have been obvious to substitute lentiviral, adeno-

associated virus, or cosmid vectors for the retroviral, plasmid, or adenoviral vectors of Eming and Sakuragawa.

Thus the invention as a whole was prima facie obvious.

Claims 1-10, 12, and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al (US Published Application 2003/0091543) in view of Sakuragawa (Cell Transplantation 4(3): 343-346, 1995) taken with the evidence of Marshall (US Patent 6479052).

This rejection is directed to a generic embodiment of the rejection which does not require an amniotic membrane. See claim 12, which recites a matrix.

Klein taught a method of modulating the delivery of a growth factor to an animal by delivering to the animal's skin a graft comprising a membrane comprising a biocompatible matrix comprising amniotic membrane cells modified to express a growth factor. See e.g. claims 4, 8, and 21. The method can be used to treat abnormal wound healing. See e.g. claim 31. Klein taught that one matrix that could be used to for grafts applied to the skin was INTEGRA, a collagen glycosaminoglycan matrix. Marshall (US Patent 6479052) disclosed at column 7, lines 19-22 that INTEGRA is a membrane.

Although Klein taught the use of amniotic cells generally, Klein did not explicitly teach the use of amniotic epithelial cells specifically.

Sakuragawa taught that human amniotic epithelial cells could be transfected by either plasmid or adenoviral vectors, and that amniotic epithelial cells do not express HLA-A, B, C and DR antigens and do not cause rejection reactions or topical

inflammation even when transplanted allogeneically. See e.g. claim 2, column 2, lines 9-13 and 27-39; column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use amniotic epithelial cells in the invention of Klein for at least two reasons. First, Klein teaches the use of amniotic cells generally, but does not teach the removal of amniotic epithelial cells from non-epithelial amniotic cells. As a result, transfection of the amniotic cells as a group would result in transfection of the amniotic epithelial cells. Second, one would have been motivated to use the epithelial cells in particular because Sakuragawa exemplified their use for expression and delivery of exogenous gene products and taught that they do not express HLA-A, B, C and DR antigens and do not cause rejection reactions or topical inflammation even when transplanted allogeneically.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/23/05 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 7-9 of the response. Applicant relies on the arguments against the Faulk and Eming references set forth in the response to the 102 rejections. These arguments are unpersuasive for the reasons set forth above. With regard to the Sakuragawa reference, Applicant argues that the

cells of Sakuragawa are transplanted subcutaneously and so are not applied to the skin as required by the claims. This argument is unpersuasive because Sakuragawa is not relied upon to teach delivery to the skin. Instead Sakuragawa provides motivation to use transfected amniotic epithelial cells to deliver the product of an exogenous gene.

Applicant asserts that the Examiner has not made the requisite showing of a suggestion to combine the references with a reasonable expectation of success, and has indulged in "picking and choosing elements" from the cited reference while impermissibly using the subject invention as a blueprint. This is unpersuasive because MPEP 2144 states that the expectation of some advantage is the strongest rationale for combining references, and the combination of the references clearly confers advantages. As stated in the rejection, one would have been motivated to modify the method of Faulk by transfecting the amniotic epithelial cells with the vector of Eming, because Eming shows that delivery of PDGF-A by transfected epithelial cells attached to a membrane results in tissue regeneration. This is a clear advantage over the method of Faulk. Further, one would have selected amniotic epithelial cells because Sakuragawa teaches that these cells can be conveniently transplanted allogeneically without rejection due to the absence of cell surface HLA class II antigens, and a much diminished amount of HLA class I antigens. This is a clear advantage over Eming. Also, as noted in the rejection, Sakuragawa demonstrates that these cells can be transfected by means of viruses or plasmids, and suggests their use in therapeutic applications involving administration of the cells to skin. Finally, using cells on an

amniotic membrane, as taught by Faulk, eliminates the step of applying cells to a synthetic membrane, thereby simplifying the procedure of Eming.

Applicant dismisses this rationale as hindsight reconstruction. However, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." See *In re* McLaughlin 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971) and MPEP 2145 (X.)(A.). Applicant has failed to successfully point to any element of the claimed invention that was gleaned from the claimed invention instead of being taught by the cited art, and has not shown why one of ordinary skill in the art at the time of the invention would not have reasonably expected to obtain the advantages discussed above from the combination of the references. Note also that MPEP 2145 (X.)(A.) states that there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness", citing Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). "For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004))." In this case one of ordinary skill in the art was aware of the immune advantages of amniotic epithelial cells, of the advantageous effect of exogenous, recombinantly supplied PDGF

on wound healing, and of the process of applying amniotic epithelial cells to wounds. As stated above in the rejection, there is no apparent structural difference between the reconstituted tissue membrane of the instant claims and the native membrane of Faulk, so there is no limitation that is not taught by the cited references, and there is adequate motivation to combine them for the reasons given above. For these reasons the rejection is maintained.

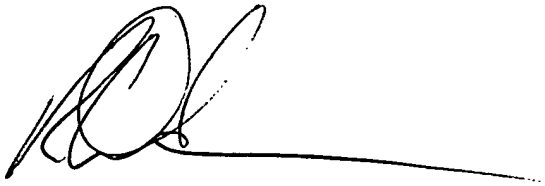
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Richard Schnizer, Ph.D.